DETAILED ACTION

This action is responsive to papers filed10/08/2009. Claims 31-33 and 36-67 are currently pending.

Claims 41-67 were withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. The requirement was made final in the first office of July 18, 2008.

Claims 31 and 39 have been amended. No claims have been newly added or newly canceled.

Claims 31-33 and 36-40 have been examined on the merits.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31-33, 36-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 31 recites the limitations of "between 0.1 and 10,000 UI/ml heparin; between 0.1 and 10,000 UI/ml protamine" in line 4 of the claim. Since the prior art measures protamine in concentration units of mg/ml which is contrary to Applicant's disclosure of UI/ml the metes and bounds of the claim are unclear as one of ordinary skill in the art measures these compounds differently.

Appropriate correction and clarification is required.

Because claims 32, 33, 36-40 depend from indefinite claim 31 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 31-33 and 36-37 remain rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Xia et al (The Journal of Immunology,2002) in view of Duggins (US 4,735,726).

Amended claim 31 is drawn to an autologous culture medium of autologous human progenitor stem cells, comprising:

a) between 0.1% and 90% of autologous human serum supplemented with between 0.1 and 10,000 UI/ml heparin and between 0.1 and 10, 000 UI/ml protamine; and

b) a base culture medium including basic nutrients wherein the autologous human serum is obtained by plasmapheresis with heparin and protamine.

Dependent claims include the treatment of the autologous serum, the source of the autologous serum, and the inclusion of an antibiotic.

Claims 31-33 and 36-37 are product-by-process claims. M.P.E.P. § 2113 reads, "Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps."

"Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted).

The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. See, e.g., *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979)

The use of 35 U.S.C. §§ 102 and 103 rejections for product-by-process claims has been approved by the courts. "[T]he lack of physical description in a product-by-process claim makes determination of the patentability of the claim more difficult, since in spite of the fact that the claim may recite only process limitations, it is the patentability of the product claimed and not of the recited process steps which must be established. We are therefore of the opinion that when the prior art discloses a product which reasonably appears to be either identical with or only slightly different than a product claimed in a product-by-process claim, a rejection based alternatively on either section 102 or section 103 of the statute is eminently fair and acceptable. As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972).

Xia et al teach a media composition that comprises AIM-V medium containing 2% autologous serum, 25 U/ml heparin and 0.125 mg/ml protamine sulfate (page 1134, figure 5, formula C). The AIM-V media inherently contains the claimed antibiotics streptomycin and gentamycin as well as basic nutrients for cell culture. While the

reference is silent with regard to the method of producing the autologous serum, it appears that the claimed autologous serum and the reference autologous serum would be structurally the same. Therefore the limitation of the autologous serum is deemed to be met by the reference.

However, even if this were not the case, obtaining autologous human serum from the blood of the patient by means of plasmapheresis is a well established and conventional procedure and therefore obvious as evidenced by Duggins who teaches that plasmapheresis is commonly used to obtain serum proteins and to produce cell culture media (background, column 1 lines 28-32). Applicant has disclosed that the use of heparin and protamine in a plasmapheresis method would have provided an autologous serum with roughly the same amounts (or similar) of heparin and protamine in the serum as claimed by Applicant (Specification page 5 para 28). The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Therefore one of ordinary skill in the art would have been motivated with a reasonable expectation of success to use plasmapheresis to obtain autologous serum for the culture medium of Xia because Duggins teaches that plasmapheresis is commonly used to obtain serum proteins and to produce cell culture media.

The concentrations of the heparin and the protamine appear to fall within the claimed concentration ranges as the units of U/ml as used by Xia for the concentration

of heparin are interpreted to be equivalent to UI/ml as used by Applicant (the U or UI standing for international units). However even if they were not the same, one of ordinary skill in the art would have been motivated to modify the concentration of the heparin either up to enhance the result of the heparin on the cells or down in order to save money and conserve resources. While the Xia et al reference uses the media composition for a different purpose, as long is there is a motivation and reasonable expectation of success to arrive at the same concentrations as claimed by Applicant, the claimed composition is deemed to be obvious. The treating of the autologous serum to inactivate a complement is also obvious as heat inactivation of serum is a well established and conventional procedure in the art of tissue culture (as acknowledged by Applicant on pages 3-4 paragraph 21).

Therefore the teaching of Xia et al anticipates or in the alternative in view of Duggins renders obvious Applicant's invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 31-33 and 36-40 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chachques (US 2002/0124855) in view of Furcht et al (US 7,015,037), Duggins (US 4,735,726) and Yang et al (US 6,624,141).

Claim 38 is drawn to the medium of claim 31, further comprising at least one of amphoterycin B and a Fibroblast Growth Factor (FGF).

Claim 39 is drawn to the medium of claim 31, and comprises: 89% HAM-F12; 10% autologous human serum of a patient supplemented with heparin between 0.1 and 100 UI/ml and protamine between 0.1 to 100 UI/ml; and 1% penicillin/streptomycin.

Claim 40 is drawn to the culture medium of claim 39, wherein the autologous human serum further comprises at least one of 0.25 mg/ml of amphoterycin B and 0.1 to 250 pg/ml of recombinant bFGF.

Chachques describes a culture medium comprising 79% Ham-F12 medium, 25 pg/ml bFGF, 20% fetal calf serum and 1% penicillin/streptomycin (page 3 para 40). The medium is intended to be used to culture myogenic cells for the repair of a damaged myocardium. Autologous cells are preferred in order to reduce the immune response (page 2 para 23-24).

Chachques does not teach the use of autologous human serum, heparin, protamine or the specific concentrations as claimed by Applicant.

Furcht et al teach a method of culturing cardiomyocytes to be used to treat cardiac diseases such as cardiomyopathy (disorder of the myocardium) (column 9 lines 30-34). The cells can either be maintained in the presence of fetal calf serum or autologous serum (column 15 lines 39-41).

Therefore one of ordinary skill in the art would have been motivated to use autologous serum in the culture medium of Chachques given that Chachques emphasizes the importance of avoiding an immune response by using autologous cells and Furcht et al also teaches that cardiac cells can be cultured with autologous serum as well as fetal calf serum. One of ordinary skill in the art would have had a reasonable

expectation of success because both Chachques and Furcht et al were culturing cardiac cells for the treatment of a damaged myocardium.

Furcht et al is silent with regard to the method of collecting the autologous serum from the patient.

Duggins teaches that plasmapheresis is commonly used to obtain serum proteins and to produce cell culture media (background, column 1 lines 28-32).

Yang et al teach that heparin is a coagulant of choice particularly in all procedures involving extracorporeal blood circulation such as plasmapheresis (background, column 1 lines 25-35). Protamine is used to neutralize the negative side-effects of heparin and Yang et al teach a specific protamine that is bioactive and has low toxitcity (column 3 lines 45-55).

Therefore one of ordinary skill in the art would have been motivated with a reasonable expectation of success to use plasmapheresis to obtain autologous serum for the culture medium of Chachques because Duggins teaches that plasmapheresis is commonly used to obtain serum proteins and to produce cell culture media. One of ordinary skill in the art would have also been motivated to use heparin as the anticoagulant in the plasmapheresis method as Yang et al teach that it is commonly known in the art to do so. One of ordinary skill in the art would have been motivated to use the specific protamines described by Yang et al in the plasmapheresis method as Yang et al teaches that they neutralize the negative side-effects of heparin and are bioactive and have low toxicity. Applicant has disclosed that the use of heparin and protamine in a plasmapheresis method would have provided an autologous serum with

roughly the same amounts (or similar) of heparin and protamine in the serum as claimed by Applicant (Specification page 5 para 28). The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

The concentrations of the ingredients in the culture medium would have been a matter of routine optimization and experimentation, the artisan of ordinary skill recognizing that the growth of the cells and the success of their therapeutic application would be affected by these concentrations and thus be result-effective variables.

Therefore the combined teachings of Chachques, Furcht et al, Duggins and Yang et al render obvious Applicant's invention as claimed.

Claims 31-33 and 36-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valerio et al (US 6,472,212) in view of Wilson et al (US 5,817,773) and Duggins (US 4,735,726).

Valerio et al describe methods and compositions for culturing primate bone marrow cells, specifically including human cells (column 26 example d). A media composition is described that comprises a base culture medium that includes basic nutrients, 5% heat inactivated autologous human serum, 4 µg/ml protamine sulfate and 100 U/ml penicillin (column 29 lines 33-40). Many different types of culture media are

taught to be suitable and commercially available and a short non-restricted list is mentioned. While Ham-F12 is not on that list, it is a media known in the prior art to be used for culturing bone marrow cells and would have been an obvious alternative. The serum amounts are taught to vary from 5 to 30% and the media compositions are taught to include one or more antibiotics as well as growth factors (column 14 lines 57-63). Streptomycin is indicated as an acceptable antibiotic for inclusion in the media composition with penicillin as well (column 24 line 44).

Valerio et al do not specifically include heparin or fibroblast growth factor (FGF) in the media composition or the manner in which the autologous serum is collected.

Duggins teaches that plasmapheresis is commonly used to obtain serum proteins and to produce cell culture media (background, column 1 lines 28-32).

Therefore one of ordinary skill in the art would have been motivated with a reasonable expectation of success to use plasmapheresis to obtain autologous serum for the culture medium of Valerio because Duggins teaches that plasmapheresis is commonly used to obtain serum proteins and to produce cell culture media. This method would have provided the serum component with any and all characteristics of the serum component of the claimed invention.

Wilson et al teach the stimulation of hematopoietic cells with fibroblast growth factor (FGF). An FGF is also taught to be used in combination with other growth factors (column 12 lines 20-25). Heparin sulfate is taught to be used to potentiate the stimulatory effect of concentrations of an FGF administered to hematopoietic cells (column 12 lines 63-66). Addition of at least one FGF in combination with heparin to a

bone marrow cell culture is taught to increase the numbers of stem cells in a population to be used for transplantation (column 17 lines 25-30). Recombinant FGFs are taught to be used as well (column 17 lines 37-62). Low concentrations of bFGF (0.2 ng/ml which is equal to 200 pg/ml) are taught to significantly enhance cell growth (column 22 lines 41-43) especially when combined with low concentrations of heparin.

Therefore one of ordinary skill in the art would have been motivated to add FGF with heparin to the media of Valerio et al because Wilson et al teach that FGF combined with heparin stimulates the growth of bone marrow cells. One of ordinary skill in the art would have had a reasonable expectation of success because both Valerio et al and Wilson et al were culturing bone marrow cells for therapeutic administration to humans.

The concentrations of the FGF and the heparin in the culture medium would have been a matter of routine optimization and experimentation, the artisan of ordinary skill recognizing that the growth of the cells, the success of their therapeutic application and the cost of the procedure would be affected by these concentrations and thus be result-effective variables.

Therefore the combined teachings of Wilson et al, Duggins and Valerio et al render obvious Applicant's invention as claimed.

Response to Arguments

Applicant's arguments filed 10/08/2009 have been fully considered but they are not persuasive. Applicant's arguments have been addressed in so far as they relate to the rejections above.

Applicant argues that the restriction requirement is not proper and should be withdrawn. Applicant asserts that the intended use of the media composition is relevant to the subject of unity of invention because depending on the intended use of the media, a variety of different components may be a result effective variable.

This is not found persuasive because the intended use of the claimed composition only requires that the composition be in a form suitable for this intended use. Since the composition of Xia is in a form suitable for the claimed intended use of expansion of human progenitor cells, the composition of Xia meets this limitation. In addition, the concentration of all components in any culture media composition, regardless of the intended use, are result effective variables since they affect the visible result of cell viability and growth.

According to 37 CFR 1.476, lack of unity of invention may be directly evident before considering the claims in relation to any prior art, or after taking the prior art into consideration, as where a document discovered during the search shows the invention claimed in a generic or linking claim lacks novelty or is clearly obvious, leaving two or more claims joined thereby without a common inventive concept. Therefore a common technical feature which is an obvious variant of a known composition can not be a special technical feature and thus unity of invention is lacking. The restriction requirement is therefore deemed to be proper and final. If Applicant can submit some

form of objective evidence that demonstrates that the Xia media composition contains structural features or components that render it incapable of performing as an expansion medium, this might prove to be persuasive.

Applicant argues that anyone skilled in the art would understand that concentration units or any similar units may be converted into other forms of units. Applicant asserts that UI and mg are readily convertible.

This is not found persuasive because Applicant has not demonstrated this by providing the conversion of UI to mg with regard to protamine. Since the Examiner has not been able to locate the conversion in the art or any measure of protamine in UI/ml, the claims are deemed to be indefinite. Evidence of this knowledge in the art would be persuasive in overcoming this rejection.

Applicant argues that the structure of the autologous serum of the present invention is different from that of Xia. Applicant asserts that the serum of Xia might have been collected in a different manner in the method of Xia as there are well known methods other than plasmapheresis that were more likely to be used by Xia and that these would create a structural difference between the serum used in Xia and the serum of the present invention. Applicant asserts that the serum in Xia must have been collected by manual drawing of blood with ACD and thus could not be the same as the serum of Applicant's invention.

This is not found persuasive because the Xia reference is silent with regard to the manner in which the serum component was collected in the reference method and any suggestions that other methods of collection of the serum were more likely are

irrelevant given that the Duggins reference provides evidence that plasmapheresis is commonly used to obtain serum proteins and to produce cell culture media (background, column 1 lines 28-32). The fact that Xia media composition may have possessed other components in addition to the claimed media components (such as sodium citrate) is permitted given that the transitional phrase of "comprising" is open-ended and allows for other components to be present. Therefore the reference media composition does not have to be structurally identical to the claimed composition in order to render it obvious. As long as there is sufficient motivation and a reasonable expectation of success for one of ordinary skill in the art to modify the reference composition to possess the same claimed limitations as the current invention, the reference teachings render the claimed invention obvious.

Applicant argues that one skilled in the art would not be motivated to raise the level of heparin in the Xia media composition up to 10,000 UI/ml as claimed by Applicant. Applicant asserts that because the concentration of heparin in the claimed media may potentially be 400 times the amount disclosed in Xia that one skilled in the art would not reasonably conclude that resources are conserved nor costs lowered.

This is not found persuasive because Applicant is claiming a concentration **range** of heparin between 0.1 and 10,000 UI/ml. The Xia heparin concentration of 25 UI/ml falls completely in this range and the motivation to lower the concentration to the lower end of Applicant's claimed range of heparin would have been to conserve resources or lower costs. The motivation to raise the concentration of heparin in the Xia media would have been to increase the effect of heparin. If some unexpected result is achieved by a

concentration of 10,000 UI.ml of heparin the claims would need to be restricted to this specific concentration and evidence of unexpected results would need to be submitted.

Applicant argues that the Furcht reference explicitly addresses the solutions for preventing immune rejection by disclosing specific approaches for transplantation to prevent immune rejection. Applicant asserts that Furcht does not include the use of autologous serum in this discussion.

This is not found persuasive because one of ordinary skill in the art would have been motivated to use autologous serum in the culture medium of Chachques given that Chachques emphasizes the importance of avoiding an immune response by using autologous cells and Furcht et al also teaches that cardiac cells can be cultured with autologous serum as well as fetal calf serum(column 15 lines 39-41). Furcht clearly demonstrates that both serum types are suitable alternatives in the art of culturing cardiac cells and Chachques clearly demonstrates that autologous materials are preferred as well.

Applicant argues that those skilled in the art will understand that progenitor stem cells are attachment dependent and that this limitation is a technical characteristic of the present invention. Applicant asserts that because Valerio and Wilson are directed to the culture of bone marrow cells that these references are not relevant.

This is not found persuasive because the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

As long as there is a motivation to combine the same ingredients into a media composition then the media composition is deemed to be obvious. Objective evidence that the media composition of Valerio would possess structural features or components that render it incapable of performing as an expansion medium for progenitor stem cells might prove to be persuasive.

Applicant asserts that the claimed media composition presents high autologous calcium content which is critical for cell attachment. Applicant asserts that the presence of autologous calcium in the media is a consequence of the novel combination of media components as that recited in claim 31. Applicant asserts that plasmapheresis with heparin and protamine results in high autologous calcium.

This is not found persuasive because claim 31 does not recite the limitation of autologous calcium nor has Applicant provided any evidence that this is an inherent feature of the claimed invention.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant again argues that the order in which the components of the media are added is critical for obtaining the specific properties of the claimed media. Applicant asserts that the specific characteristics are technical in character and specifically make the media suitable for expanding progenitor cells.

This is not found persuasive because the argument is merely the argument of counsel and is unsupported by evidence or declarations of those skilled in the art. Counsel's arguments cannot take the place of objective evidence. *In re Schulze*, 145 USPQ 716 (CCPA 1965); *In re Cole*, 140 USPQ 230 (CCPA 1964): and especially *In re Langer*, 183 USPQ 288 (CCPA 1974). Applicant's reference to the references cited in the Spec at paragraph 6 and Xia are not deemed to be persuasive as they do not demonstrate that the claimed media can not be made in another manner or that the prior art compositions are incapable of meeting the claimed limitations.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA SCHUBERG whose telephone number is (571)272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford/
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